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Brief Original Report

Implications of lower risk thresholds for statin treatment in primary prevention: Analysis of CPRD and simulation modelling of annual cholesterol monitoring

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ABSTRACT

Objective: To estimate numbers affected by a recent change in UK guidelines for statin use in primary prevention of cardiovascular disease.

Method: We modelled cholesterol ratio over time using a sample of 45,151 men (≥ 40 years) and 36,168 women (≥ 55 years) in 2006, without statin treatment or previous cardiovascular disease, from the Clinical Practice Research Datalink. Using simulation methods, we estimated numbers indicated for new statin treatment, if cholesterol was measured annually and used in the QRISK2 CVD risk calculator, using the previous 20% and newly recommended 10% thresholds.

Results: We estimate that 58% of men and 55% of women would be indicated for treatment by five years and 71% of men and 73% of women by ten years using the 20% threshold. Using the proposed threshold of 10%, 84% of men and 90% of women would be indicated for treatment by 5 years and 92% of men and 98% of women by ten years.

Conclusion: The proposed change of risk threshold from 20% to 10% would result in the substantial majority of those recommended for cholesterol testing being indicated for statin treatment. Implications depend on the value of statins in those at low to medium risk, and whether there are harms.

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Introduction

Lipid modification guidelines for cardiovascular disease (CVD) prevention recommend that patients who are deemed to be at high risk of CVD should be prescribed statins to lower their LDL-cholesterol (Cooper et al., 2010). In the UK, high risk is currently assessed using 10-year CVD risk equations that contain a combination of demographic and clinical risk factors, including the ratio of total to HDL-cholesterol (Anderson et al., 1991; Hippisley-Cox et al., 2008; Woodward et al., 2007). Until recently, treatment was indicated if the calculated risk score exceeds 20% (Cooper et al., 2010). In 2014 the National Institute for Health and Care Excellence (NICE) recommended reducing the threshold for treatment to 10% (National Institute for Health and Care Excellence, 2014). If implemented, this decision would lead to an increase in the number of individuals indicated for treatment; while it has been suggested that millions of patients may be affected (Price, 2014; Thompson et al., 2014), estimated numbers have not been published. We therefore evaluate cholesterol testing and associated CVD

risk prediction, in primary prevention patients representative of those attending monitoring in UK general practice, to estimate the number indicated for treatment under monitoring schemes using the previous 20% and the newly recommended 10% risk thresholds. Cholesterol, like most biochemical markers, is measured with biological variability as well as assay variability, in the sense that two cholesterol measurements on the same person will rarely give exactly the same result. This uncertainty in cholesterol measurements will translate into uncertainty in calculated CVD risk estimates. We therefore include in our model a distinction between true CVD risk, based on underlying, usual cholesterol ratio, and observed or estimated CVD risk, based on the cholesterol ratio in a blood sample taken at a particular clinic visit.

Methods

Data were a sample of 45,151 men aged over 40 years and 36,168 women aged over 55 years, without previous CVD and statin treatment, from the Clinical Practice Research Datalink (CPRD) (CPRD, 2013). Age was restricted to the earliest monitoring age in the NHS Health Check programme (NHS Choices, 2014) to minimise potential cholesterol changes throughout menopause (Bittner, 2009; Matthews et al., 2009). We use a random-effects model to estimate the between-subject variation, the average rate of change over time and its variation between individuals, and the short-term variability in

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any single measurement (Stevens et al., 2010). We used previously published simulation methods (Stevens et al., 2010) to estimate the number of men and women who would be indicated for new statin treatment if their cholesterol was measured annually and used in the QRISK2 CVD risk calculator (Hippisley-Cox et al., 2008), using the previous threshold of 20% and the new threshold of 10%. We assumed annual measurement because the median (interquartile range) time between cholesterol measurements for individuals in our CPRD sample with more than one test was 1.02 (0.56–1.65) years. We used estimates of within-measurement variability to model the relationship between the observed and the underlying, usual cholesterol ratio, and hence distinguish true CVD risk from estimated CVD risk. We estimate the distribution of true CVD risk amongst those with estimated CVD risk above threshold. Stata 12.1 (StataCorp, 2011) was used for all analyses.

Results

The mean (SD) age, total to HDL-cholesterol ratio and systolic blood pressure were 60.3 (12.0) years, 4.3 (1.3) and 139 (18) mm Hg in men and 68.5 (9.0) years, 3.8 (1.1) and 142 (19) mm Hg in women. The prevalence of diabetes was 13.4% in men and 9.9% in women. Approximately one third of men (35.4%) and half of women (49.8%) were non-smokers; 45.2% of men and 36.8% of women were ex-smokers; and 19.4% of men and 13.5% of women currently smoked (5.3%, 7.3% and 6.8% of men and 4.7%, 5.1% and 3.7% of women were light, moderate and heavy smokers respectively, as defined in QRISK2) (Hippisley-Cox et al., 2008).

The estimated SD of the within-measurement variability in total to HDL-cholesterol ratio was 0.37 in men and 0.23 in women: that is, (for example) within an individual man, the measured cholesterol ratio on any given clinic visit can vary by ± 0.37 (SD) or ± 0.73 (normal range) around his usual value.

On average there was little change in cholesterol ratio over time: mean change across all men in the cohort was -0.001 (95%CI -0.004 to 0.002) per year and mean change across all women in the cohort was 0.002 (95%CI -0.001 to 0.004) per year. However, individuals varied greatly around these averages: the SD of rate of change was 0.097 per year in men and 0.090 per year in women. (Thus, for 95% of men, rate of change lies between a 0.19 per year decrease and a 0.19 per year increase. Similarly for 95% of women, rate of change lies between a 0.17 per year decrease and a 0.18 per year increase.)

Table 1 shows the estimated numbers indicated for treatment per 10,000 under the assumption that cholesterol ratio is measured annually and that treatment is indicated if QRISK2 score exceeds 20%, as in previous guidelines. We estimate that 58% of men and 55% of women would be indicated for treatment by five years and 71% of men and 73% of women by ten years. Table 1 also shows, in these men and women with estimated risk above 20%, the modelled distribution of true CVD risks; only a small number of those indicated for treatment had true risk below 20% and none had true risk below 15%.

Table 2 shows the corresponding results, under the assumption that treatment is indicated if QRISK2 score exceeds 10%, as recommended in the new guidelines. We estimate that 84% of men and 90% of women would be indicated for treatment by 5 years and 92% of men and 98% of women by ten years. Of those indicated for treatment, few had true risk below 10% and (data not shown) none had true risk below 5%.

Discussion

The recent change of risk threshold from 20% to 10% would result in the substantial majority of men and women above the recommended age for cholesterol testing being indicated for statin treatment. However, using mathematical modelling we estimate that only a small proportion of those indicated for treatment would be due to false positive tests, and that these are primarily amongst those close to the threshold whether this is at 20% or 10%.

In the absence of large randomised trials powered to compare cardiovascular risk assessment at different thresholds, we have used established

Table 1

Men and women from the Clinical Practice Research Datalink in 2006 indicated for new statin treatment when 10-year CVD risk is estimated annually with QRISK2 and compared to threshold of 20% (previous guidelines for primary prevention). Bold font denotes those whose true CVD risk is concordant with their estimated risk.

Years since first test	Cumulative number indicated for treatment per 10,000	True CVD risk amongst those indicated for treatment, cumulative number per 10,000			
		<10%	10 to <15%	15 to <20%	≥20%
<i>Men</i>					
0	4151	0	0	149	4002
1	4581	0	0	210	4371
2	4913	0	0	227	4686
3	5221	0	0	227	4993
4	5520	0	0	225	5295
5	5810	0	0	220	5590
6	6090	0	0	211	5878
7	6357	0	0	205	6152
8	6612	0	0	199	6414
9	6861	0	0	193	6667
10	7103	0	0	188	6915
<i>Women</i>					
0	3778	0	0	103	3675
1	4152	0	0	132	4020
2	4477	0	0	139	4338
3	4801	0	0	143	4658
4	5127	0	0	143	4984
5	5463	0	0	144	5319
6	5815	0	0	151	5664
7	6178	0	0	154	6024
8	6555	0	0	158	6397
9	6938	0	0	157	6781
10	7320	0	0	151	7169

modelling methods and data representative of routine general practice in the UK. One limitation of these analyses is the (unlikely) assumption that CVD risk factors other than age and cholesterol level remain constant over time. We have also not attempted to model the complexity of individual

Table 2

Men and women from the Clinical Practice Research Datalink in 2006 indicated for new statin treatment when 10-year CVD risk is estimated annually with QRISK2 and compared to threshold of 10% (new guidelines for primary prevention). Bold font denotes those whose true CVD risk is concordant with their estimated risk.

Years since first test	Cumulative number indicated for treatment per 10,000	True CVD risk amongst those indicated for treatment, cumulative number per 10,000			
		<10%	10 to <15%	15 to <20%	≥20%
Men					
0	7167	95	1409	1484	4179
1	7468	115	1401	1487	4466
2	7709	116	1366	1464	4763
3	7935	110	1339	1421	5065
4	8150	104	1312	1370	5365
5	8352	96	1279	1319	5657
6	8540	92	1232	1273	5943
7	8721	88	1181	1239	6213
8	8891	82	1124	1212	6473
9	9050	77	1063	1185	6725
10	9199	72	1005	1150	6972
Women					
0	7336	117	1957	1466	3795
1	7737	119	2034	1485	4099
2	8073	111	2043	1509	4410
3	8388	108	2004	1546	4729
4	8690	100	1936	1595	5059
5	8969	88	1843	1643	5394
6	9220	75	1727	1676	5741
7	9431	59	1591	1676	6105
8	9603	47	1428	1646	6481
9	9736	35	1244	1590	6867
10	9834	24	1044	1511	7255

treatment decision making, however the analyses presented here aim to form the basis for evaluation of national monitoring strategies.

Implications depend on the value of statins in those at low to medium risk, and whether there are harms. The extensive literature on non-cardiovascular effects of statins has recently been reviewed (Desai et al., 2014): the best documented harms include an increased risk of diabetes, for example (Rajpathak et al., 2009; Sattar et al., 2010). Recent systematic reviews (Finegold et al., 2014; Ganga et al., 2014) found no increase in muscle problems in statin groups compared to placebo groups across randomised trials; however two trials not included in those reviews did find such effects (Golomb et al., 2012; Parker et al., 2013). Beyond actual and putative harms of treatment, it is not known whether there are other harms associated with monitoring: a harm associated with 'labelling' has been found for hypertension (Hamer et al., 2010). If we accept the conclusions published by the Cholesterol Treatment Trialists' Collaboration (Mihaylova et al., 2012) that statins have net benefit in those at low risk, then the shift to a lower threshold corresponds to the extension of a treatment, from which almost all middle-aged men and women stand to benefit, to an increasingly high percentage of the population.

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Conflict of interest statement

The authors declare that there are no conflicts of interests.

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References

- Anderson, K.M., Odell, P.M., Wilson, P.W.F., Kannel, W.B., Framingham, M.P.H., 1991. Cardiovascular disease risk profiles. *Am. Heart J.* 121, 293–298.
- Bittner, V., 2009. Menopause, age, and cardiovascular risk: a complex relationship. *J. Am. Coll. Cardiol.* 54, 2374–2375. <http://dx.doi.org/10.1016/j.jacc.2009.10.008>.

- Cooper, A., Nherera, L., Calvert, N., et al., 2010. Clinical Guidelines and Evidence Review for Lipid Modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. NICE, London.
- CPRD, 2013. Clinical Practice Research Datalink [WWW Document]. Crown Copyr. URL, <http://www.cprd.com/home/> (accessed 7.15.14).
- Desai, C.S., Martin, S.S., Blumenthal, R.S., 2014. Non-cardiovascular effects associated with statins. *BMJ* 349, g3743. <http://dx.doi.org/10.1136/bmj.g3743>.
- Finegold, J.A., Manisty, C.H., Goldacre, B., Barron, A.J., Francis, D.P., 2014. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur. J. Prev. Cardiol.* 21, 464–474. <http://dx.doi.org/10.1177/2047487314525531>.
- Ganga, H.V., Slim, H.B., Thompson, P.D., 2014. A systematic review of statin-induced muscle problems in clinical trials. *Am. Heart J.* 168, 6–15. <http://dx.doi.org/10.1016/j.ahj.2014.03.019>.
- Golomb, B.A., Evans, M.A., Dimsdale, J.E., White, H.L., 2012. Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial. *Arch. Intern. Med.* 172, 1180–1182. <http://dx.doi.org/10.1001/archinternmed.2012.2171>.
- Hamer, M., Batty, G.D., Stamatakis, E., Kivimaki, M., 2010. Hypertension awareness and psychological distress. *Hypertension* 56, 547–550. <http://dx.doi.org/10.1161/HYPERTENSIONAHA.110.153775>.
- Hippisley-Cox, J., Coupland, C., Vinogradova, Y., et al., 2008. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 336, 1475–1482. <http://dx.doi.org/10.1136/bmj.39609.449676.25>.
- Matthews, K.A., Crawford, S.L., Chae, C.U., et al., 2009. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J. Am. Coll. Cardiol.* 54, 2366–2373. <http://dx.doi.org/10.1016/j.jacc.2009.10.009>.
- Mihaylova, B., Emberson, J., Blackwell, L., et al., 2012. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 380, 581–590. [http://dx.doi.org/10.1016/S0140-6736\(12\)60367-5](http://dx.doi.org/10.1016/S0140-6736(12)60367-5).
- National Institute for Health and Care Excellence, 2014. NICE Clinical Guideline 181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease.
- NHS Choices, 2014. Your NHS Health Check guide [WWW Document]. URL, <http://www.nhs.uk/Conditions/nhs-health-check/Pages/What-is-an-NHS-Health-Check.aspx> (accessed 10.29.14).
- Parker, B.A., Capizzi, J.A., Grimaldi, A.S., et al., 2013. Effect of statins on skeletal muscle function. *Circulation* 127, 96–103. <http://dx.doi.org/10.1161/CIRCULATIONAHA.112.136101>.
- Price, C., 2014. Majority of GPs reject NICE proposals to extend statins to millions more [WWW Document]. Pulse Today (URL http://www.pulsetoday.co.uk/clinical/therapy-areas/cardiovascular/majority-of-gps-reject-nice-proposals-to-extend-statins-to-millions-more/20005985.article#U6ATW_ISbIV (accessed 7.15.14)).
- Rajpathak, S.N., Kumbhani, D.J., Crandall, J., Barzilai, N., Alderman, M., Ridker, P.M., 2009. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care* 32, 1924–1929. <http://dx.doi.org/10.2337/dc09-0738>.
- Sattar, N., Preiss, D., Murray, H.M., et al., 2010. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 375, 735–742. [http://dx.doi.org/10.1016/S0140-6736\(09\)61965-6](http://dx.doi.org/10.1016/S0140-6736(09)61965-6).
- StataCorp, 2011. Stata Statistical Software: Release 12.1.
- Stevens, R.J., Oke, J., Perera, R., 2010. Statistical models for the control phase of clinical monitoring. *Stat. Methods Med. Res.* 19, 394–414. <http://dx.doi.org/10.1177/0962280209359886>.
- Thompson, R., Gerada, C., Haslam, D., et al., 2014. Concerns about the latest NICE draft guidance on statins [WWW Document]. URL, http://www.nice.org.uk/media/877/AC/NICE_statin_Jetter.pdf (accessed 6.17.14).
- Woodward, M., Brindle, P., Tunstall-Pedoe, H., 2007. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 93, 172–176. <http://dx.doi.org/10.1136/hrt.2006.108167>.